Differential Contribution of Dead Space Ventilation and Low Arterial \( pCO_2 \) to Exercise Hyperpnea in Patients With Chronic Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

Roland Wensel, MD, Panagiota Georgiadou, MD, Darrel P. Francis, MA, MRCP, Stephanie Bayne, Adam C. Scott, PhD, Sabine Genth-Zotz, MD, Stefan D. Anker, MD, PhD, Andrew J.S. Coats, DM, and Massimo F. Piepoli, MD, PhD

In chronic heart failure (CHF), the abnormally large ventilatory response to exercise (VE/VCO\(_2\) slope) has 2 conceptual elements: the requirement of restraining arterial partial pressure of carbon dioxide (pCO\(_2\)) from increasing (because of an increased ratio between increased physiologic dead space and tidal volume [VD/VT]) and the depression of arterial pCO\(_2\) by further increased ventilation, which necessarily implies an important non-carbon dioxide stimulus to ventilation. We aimed to assess the contribution of these 2 factors in determining the elevated VE/VCO\(_2\) slope in CHF. Thirty patients with CHF underwent cardiopulmonary exercise testing (age 65 ± 11 years, left ventricular ejection fraction 34 ± 15%, peak oxygen uptake 15.2 ± 4 ml/kg/min, VE/VCO\(_2\) slope 36.4). At rest and during exercise, arterial pCO\(_2\) was measured and VD was calculated and separated into serial and alveolar components. VD/VT decreased from 0.57 at rest to 0.44 at peak exercise (p < 0.01). VE/VCO\(_2\) slope was correlated with peak exercise VD/VT (r = 0.67), the serial VD/VT ratio (r = 0.64), and alveolar VD/VT ratio (r = 0.51) at peak exercise (all p < 0.01). VE/VCO\(_2\) slope was also correlated with arterial pCO\(_2\) (r = −0.75, p < 0.001). Despite this, arterial pCO\(_2\) was not related to peak oxygen uptake (r = 0.2) or to arterial lactate (r = −0.25) and only weakly to New York Heart Association functional class (F = 3.7). First, the increased VE/VCO\(_2\) slope was caused by both the high VD/VT ratio and by other mechanisms, as shown by low arterial pCO\(_2\) during exercise. Second, this latter component (depression of arterial pCO\(_2\)) was not related to conventional measures of heart failure severity. ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;93:318–323)
METHODS

Patients: We studied 30 patients (Table 1) (ages 65 ± 11 years; left ventricular ejection fraction 34 ± 15%; 29 men) with CHF due to ischemic heart disease (n = 22) or dilated cardiomyopathy (n = 8). New York Heart Association (NYHA) functional classification showed 5 patients in class I, 14 in class II, and 11 in class III. Forced expiratory 1-second volume and forced vital capacity were 79 ± 17% and 86 ± 16% of predicted values, respectively. Patients’ medications included angiotensin-converting enzyme inhibitors (n = 25), angiotensin II receptor antagonists (n = 5), β blockers (n = 18), amiodarone (n = 5), loop diuretics (n = 25), spironolactone (n = 10), aspirin (n = 16), digitalis (n = 5), hydroxymethylglutaryl coenzyme A-reductase inhibitors (statins; n = 17), nitrates (n = 7), and warfarin (n = 11). Medication had been constant for ≈6 weeks before the study. An age-matched group of 39 healthy volunteers (Table 1) was studied to show how the VE/VCO2 relation during exercise behaves in subjects without heart failure. The local ethics committee has approved the study protocol, which conformed to the protocols of the Declaration of Helsinki. All patients gave written informed consent.

Exercise testing: After 5 minutes of standing at rest, a symptom-limited treadmill cardiopulmonary exercise test was performed in all patients. We used the modified Naughton protocol, which is an incremental test with stages of 2 minutes and increments in both slope and velocity of the treadmill that simulate an increment of ≈1 MET (≈3.5 ml oxygen · kg⁻¹ · min⁻¹) per stage. Pulmonary gas exchange was analyzed using a metabolic cart consisting of a flowmeter and a mass spectrometer (AMIS 2000, Innovision, Odense, Denmark). Patients breathed through a mouthpiece (volume 35 ml). Raw data (flow, oxygen and carbon dioxide concentrations) were stored for later offline breath-by-breath analysis of gas exchange and calculation of serial dead space. Peak oxygen uptake was defined as the highest 30-second average of oxygen uptake in the last minute of exercise. The anaerobic threshold was calculated using the V-slope method. When no clear kink in the VCO2/VO2 relation was observed, the start of the increase in end tidal pO2 and the increase of the ventilatory equivalent for oxygen were used to determine the anaerobic threshold. VE/VCO2 ratios were calculated at rest, at the anaerobic threshold, and at peak exercise. The VE/VCO2 slope was measured as the slope of the linear regression relating ventilation to VCO2.⁴

Measurement of dead space ventilation: A 20-gauge arterial catheter (Leader; Vygon, Ecoven, France) was inserted into the radial artery. Arterial blood samples were obtained at rest and during the second minute of each stage of exercise. Each sample was drawn over a period of approximately 10 seconds, and when the respiratory rate was <30/min, special care was taken to draw the sample over an integral number of respiratory cycles. Arterial blood gases, lactate, and hydrogen ion concentrations were measured with electrodes by standard methods, and physiologic VD was calculated from gas exchange and arterial pCO₂. Serial dead space was measured from the expiratory capnogram using the modified Fowler technique.⁹,¹⁰ In brief, this method consists of construction of a sharp boundary between serial dead space and alveolar gas by graphic integration. Alveolar dead space was then defined as the difference between physiologic and serial dead space. The ratio of VD/VT, between VD and VT, was then calculated.

Statistical analysis: Data are shown as mean ± SD. The changes in the parameters during exercise have been analyzed by repeated-measures analysis of variance. The patient dead space to tidal volume ratios, arterial pCO₂, lactate and hydrogen ion concentrations were correlated with VE/VCO₂ ratio, VE/VCO₂ slope and peak oxygen uptake using the Pearson correlation. When data did not follow normal distribution the median value is shown and Friedman repeated measures analysis of variance on ranks and the Spearman correlation was used, respectively. Differences in VD/VT and arterial pCO₂ with respect to NYHA class were analyzed with an analysis of variance. A p value <0.05 was considered significant.

RESULTS

The results of the exercise tests are given in Tables 1 and 2. Compared with normal controls, patients with heart failure had a higher VE/VCO₂ slope and higher VE/VCO₂ ratios throughout the exercise test. In both groups the VE/VCO₂ ratios significantly decreased from at rest to the anaerobic threshold. From the anaerobic threshold to peak exercise, no further reduction occurred in both groups.

**Contribution of VD/VT and arterial pCO₂ to the ventilatory response in heart failure:** We examined whether the exercise ventilatory response was related to VD (which would support the inefficiency of gas exchange hypothesis) or to arterial pCO₂ (which would support the primary hyperventilation hypothesis).

At rest, the VE/VCO₂ ratio correlated significantly only with the VD/VT ratio (r = 0.75, p <0.001) but not with arterial pCO₂ (r = −0.36, p = 0.053). On multiple linear regression analysis, VD/VT and arte-


At the anaerobic threshold, the VE/VCO₂ ratio correlated clearly with the VD/VT ratio (r = 0.51, p < 0.005) and at peak exercise were not correlated with a high VE/VCO₂ slope (r = 0.04), to low arterial pCO₂ (r = −0.25, p = 0.2), or to the increase in the VE/VCO₂ ratio from the anaerobic threshold to peak exercise (r = −0.004). In contrast, plasma hydrogen ion concentrations showed a significant tendency to be lower in patients with higher VE/VCO₂ slopes (r = −0.46, p < 0.05) or lower arterial pCO₂ at peak exercise (r = 0.43, p < 0.05).

The same relation was seen at the anaerobic threshold (lactate vs VE/VCO₂ slope: r = −0.19, p = 0.3; lactate vs arterial pCO₂: r = 0.14, p = 0.45; hydrogen vs VE/VCO₂ slope: r = −0.42, p < 0.05; hydrogen vs arterial pCO₂: r = 0.41, p < 0.05). The increase in arterial lactate concentrations from the anaerobic threshold to peak exercise was correlated with the concomitant decrease in arterial pCO₂ (r = −0.43, p < 0.05) but not with the concomitant increase in VE/VCO₂ ratio (r = −0.09).

Relative contribution of the serial and alveolar components of physiologic dead space: At rest, the VE/VT was 0.57 ± 0.1 (range 0.28 to 0.8), which consisted of a serial dead space to VT ratio of 0.26 ± 0.06 and an alveolar dead space to VT ratio of 0.31 ± 0.08. During exercise, VE/VT decreased to 0.44 ± 0.1 at the anaerobic threshold (p < 0.05 vs rest) with no further reduction at peak exercise (0.44 ± 0.1, p < 0.05 vs rest, p = 0.9 vs anaerobic threshold). The change at the anaerobic threshold resulted from a reduction of both serial (to 0.20 ± 0.04, p < 0.05 vs rest) and alveolar (to 0.25 ± 0.07, p < 0.05 vs rest) components of the VT ratio. There was no significant change in these components between the anaerobic threshold and peak exercise, although they remained significantly different from at rest (serial dead space to VT ratio 0.19 ± 0.04; alveolar dead space to VT ratio 0.26 ± 0.07, both p < 0.05 vs rest).

VE/VCO₂ slope was correlated not only with VE/VT at peak exercise (r = 0.67, p < 0.001) and at the anaerobic threshold (r = 0.51, p < 0.01) but also with serial dead space to VT ratio (r = 0.64, p < 0.0001 and r = 0.45, p < 0.05, respectively) and

---

**FIGURE 1.** Relation between (A) arterial pCO₂ and VE/VCO₂ slope; (B) VD/VT and VE/VCO₂ slope; (C) arterial pCO₂ and peak oxygen uptake; and (D) VD/VT and peak oxygen uptake.

**FIGURE 2.** Relation between peak oxygen uptake and VE/VCO₂ slope.
with the alveolar dead space to VT ratio (r = 0.51, p < 0.01 and r = 0.42, p < 0.05, respectively). A high serial dead space to VT ratio at peak exercise had 2 contributing factors; VE/VCO₂ slope was correlated low VT (r = −0.44, p < 0.05) and showed a trend toward higher serial dead space (r = 0.33, p = 0.076).

**DISCUSSION**

In our study, patients with a higher VE/VCO₂ slope had both an increased VD/VT ratio and lower arterial carbon dioxide during exercise. This cannot be explained by isolated inefficiency of gas exchange, which would cause the former, but certainly not the latter. Nor can it be explained by an isolated primary hyperventilation during exercise, (which would cause the latter, but not directly cause the former. Thus, the abnormally high ventilatory response in patients with steep VE/VCO₂ slopes may most plausibly result from a combination of gas exchange inefficiency (synonymous with an increase in VD/VT) and a primary increase in ventilatory drive on exercise (synonymous with a decrease in arterial pCO₂).

Ventilatory response to exercise is often measured as the slope of the VE/VCO₂ relation, because this relation is almost linear, and, therefore, the VE/VCO₂ slope provides a stable measure of the required increase in ventilation for an increase in carbon dioxide output during exercise. However, as evident from our data and that of others, the VE/VCO₂ ratio changes considerably during exercise (Table 2 and Figure 3), and the VE/VCO₂ relation is not linear (Figure 4). The change of the VE/VCO₂ ratio during exercise results from corresponding changes of the VD/VT ratio and arterial pCO₂. The VE/VCO₂ slope gives a single value for the potentially complex VE/VCO₂ relation during exercise. Because it is a simplification, it is of limited value in delineating the mechanisms that determine the VE/VCO₂ ratio at different stages of exercise. At rest and during aerobic exercise, the VE/VCO₂ ratio is predominantly related to the VD/VT ratio. As anaerobic metabolism ensues, the hyperventilatory response affects the VE/VCO₂ ratio, and the 2 variables are clearly related at peak exercise. Despite being present only during anaerobic exercise, hyperventilation leads to an increase in the overall VE/VCO₂ slope, and, consequently, there is a significant relation between VE/VCO₂ slope and the degree of hyperventilation.

Our data (Figure 1) can be reconciled with previous studies that seemed to reject the possibility of a primary hyperventilatory mechanism; the answer may lie in Figure 1. If a primary hyperventilatory mechanism were present, the arterial pCO₂ would be expected to be low in the affected patients. Previous studies have examined this low arterial carbon dioxide level, but sought a correlation with peak oxygen uptake or NYHA class; these studies found no significant relation and thus rejected the hypothesis. However, the primary hyperventilation hypothesis predicts only that low arterial carbon dioxide would correlate with high ventilatory responses (namely, VE/VCO₂ slope). It does not directly predict whether there should be a relation between arterial carbon dioxide and either peak oxygen uptake or NYHA class. Our finding that arterial pCO₂ is lower in patients with increased VE/VCO₂ slope (Figure 1) confirms the existence of a primary hyperventilatory mechanism. It may at first seem surprising that arterial pCO₂ was correlated with VE/VCO₂ slope but not with peak oxygen uptake when the latter were generally highly correlated, as seen in this study (Figure 2). However, the physiopathologic mechanisms responsible for VE/VCO₂ slope and the peak oxygen uptake are not identical. The fact that arterial pCO₂ correlates with VE/VCO₂ slope and not with peak oxygen uptake, indicates that even although arterial pCO₂ is not significantly linked to “conventional severity,” it still varies from patient to patient, and this variation covar-

**TABLE 2**  VE/VCO₂, Arterial pCO₂, Lactate, and pH at Different Stages of Exercise

<table>
<thead>
<tr>
<th></th>
<th>At Rest</th>
<th>Anaerobic Threshold</th>
<th>Peak Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VCO₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>59.7*</td>
<td>41.8*†</td>
<td>40.7*‡</td>
</tr>
<tr>
<td>Controls</td>
<td>34</td>
<td>27*</td>
<td>29*</td>
</tr>
<tr>
<td>Arterial pCO₂ (mm/Hg)</td>
<td>37.1 ± 5</td>
<td>38.0 ± 4.4</td>
<td>36.5 ± 5.3</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.99 ± 0.35</td>
<td>1.6 ± 0.4*</td>
<td>4.1 ± 1.7*</td>
</tr>
<tr>
<td>pH</td>
<td>7.424 ± 0.04</td>
<td>7.411 ± 0.04</td>
<td>7.393 ± 0.05†</td>
</tr>
</tbody>
</table>

*p < 0.05 versus at rest; †p < 0.05 versus anaerobic threshold; ‡p < 0.05 versus at rest and anaerobic threshold; †‡p < 0.05 versus healthy controls.

No blood gas data were obtained from the control group.

**FIGURE 3.** Time course of the VE/VCO₂ ratio during the incremental exercise test in 1 patient. The VE/VCO₂ ratio is relatively stable at rest (phase I), starts to decrease at the beginning of exercise and reaches a plateau (phase II), and increases again toward the end of exercise (phase III).
ries with VE/VCO₂ slope. In other words, arterial pCO₂ has a specific link to VE/VCO₂ slope that is not the result of confounding by conventional markers of disease severity.

What is the origin of the primary hyperventilatory stimulus that decreases the arterial pCO₂ in some patients? Hyperventilation becomes a relevant factor only once anaerobic metabolism increases, suggesting that it does not result from the volitional aspects of exercise but from the systemic or local (muscular) accumulation of anaerobic metabolites. Decreased aerobic exercise capacity and early development of systemic lactic acidosis is characteristic of patients with heart failure. However, we observed no significant relation between arterial pCO₂ and plasma lactate levels at peak exercise. Patients with a lower arterial pCO₂ had a lower (rather than higher) hydrogen ion concentration. These findings are evidence against systemic lactic acidosis as the key drive to excess ventilation. An alternative stimulus to excess ventilation is activation of the muscle metaboreflex (ergoreflex), which has been shown to stimulate ventilation.

Recently, we found that accumulation of hydrogen in the skeletal muscle during exercise is a major trigger of the ergoreflex afferents (located in the muscular interstitium), and prevention of this accumulation completely abolished the ergoreflex-mediated ventilatory response to exercise. Interstitial muscular concentrations of lactate and hydrogen differ considerably from concentrations in arterial blood. Hence, arterial lactate accumulation might coincide with the start of ergoreflex activation during exercise without predicting the magnitude of the ergoreflex response.

Although the mechanism remains uncertain, it can be concluded that hyperventilation contributes to the enhanced ventilatory response to exercise in heart failure.

Our data confirm that it is the alveolar component that is the major contributor to the high VD/VT ratio in patients with heart failure. It has been proposed that this may result from suboptimal distribution of blood flow to alveoli (ventilation/perfusion mismatch). In our study, we observed that only the peak exercise alveolar VD/VT ratio was correlated with VE/VCO₂ slope; the values at rest did not. This implies that the pattern of ventilation/perfusion mismatch at rest is not a useful predictor of exercise response. It is noteworthy that high VE/VCO₂ slope is related to a lower cardiac output during exercise. High VE/VCO₂ slopes have been related to pulmonary vasoconstriction and pulmonary hypertension in CHF. The high VE/VCO₂ slope in patients with CHF results from the combination of increased VD ventilation, which is related to impaired pulmonary hemodynamics and augmented hyperventilation, which is related to the peripheral changes that occur in the characteristic of the syndrome of CHF. This underlying pathophysiology explains the outstanding value of the VE/VCO₂ slope in the assessment of disease severity and prognosis of patients with CHF.

4. Chua TP, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity


